

# Diagnosis and management of hypersensitivity pneumonitis

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## ABSTRACT

*Hypersensitivity pneumonitis (HP) is an interstitial lung disease that occurs in individuals who are genetically susceptible and who have an exaggerated immune reaction to inhaled environmental antigens. Persistent inflammation may lead to the development of lung fibrosis, which adversely affects survival. Diagnostic evaluation includes assessment of exposure history, serologic testing for precipitating antigens, high-resolution computed tomography, bronchoalveolar lavage cellular analysis, and histopathology. Multidisciplinary discussion among expert subspecialists is essential for confirming an accurate diagnosis and for determining the need for a lung biopsy. The primary treatment strategy involves avoidance of the precipitating antigen, which is associated with a mortality benefit. Pharmacotherapy includes corticosteroids, azathioprine, mycophenolate mofetil, and rituximab, although their use is supported by limited evidence. In cases of patients with fibrotic HP, nintedanib and lung transplantation may be considered. Additional research is needed to create validated environmental questionnaires, improve serologic testing for responsible antigens, and optimize timing and duration of effective pharmacological therapies.*

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**H**ypersensitivity pneumonitis (HP) is an immune-mediated inflammatory disease that affects the lung parenchyma and small airways. In some patients, persistent inflammation can lead to the development of fibrosis. HP occurs in individuals who are genetically susceptible and who exhibit an exaggerated immune response to inhaled antigens.<sup>1,2</sup> It is the third most common interstitial lung disease (ILD), with a prevalence of 1.67–2.71 per 100,000 persons in the United States and a mean age of 52 years.<sup>5</sup> The disease was first described as farmer's lung in the early 1990s, due to bacteria or mold exposure from crops.<sup>2</sup> Since then, numerous inciting agents, including avian proteins, feathers, chemicals, other molds and bacteria, have been identified. Exposures may occur in patients' homes or workplaces or during

recreational activities.<sup>2,3</sup> This brief review, adapted from an invited lecture given at the Eastern Pulmonary Conference in September 2024, discusses the updated classification, pathophysiology, diagnostic evaluation, and treatment of HP.

## METHODS

A narrative literature review was performed through PubMed to provide support for this article by using search terms that included "hypersensitivity pneumonitis," "nonfibrotic hypersensitivity pneumonitis," "fibrotic hypersensitivity pneumonitis," "antigen avoidance," "high resolution computed tomography," "bronchoalveolar lavage cellular analysis," "lung biopsy," and others. Search terms were used alone and in combination to identify relevant articles published within the past 20 years.

## CLINICAL PRESENTATION AND CLASSIFICATION

HP is a heterogeneous disease, with variations in clinical presentation, histopathologic findings, radiographic patterns, and outcomes.<sup>4</sup> Common symptoms include cough, dyspnea, wheezing, fever, chills, and fatigue. Lung examination may be normal or reveal inspiratory squeaks or crackles.<sup>1,4,5</sup> Histologic and radiographic features can vary based on the stage of disease and among individuals.<sup>1</sup> The prognosis is also variable, ranging from full recovery after antigen removal to death from end-stage fibrotic lung disease.<sup>1,6,7</sup> The median time from diagnosis to lung transplantation or death has been reported to be ~12 years.<sup>3,8</sup> HP has historically been classified as acute, subacute, or chronic. Acute HP typically presents within a few hours of exposure, and symptoms improve within hours to days. Symptoms can be difficult to distinguish from respiratory viral illness but may recur

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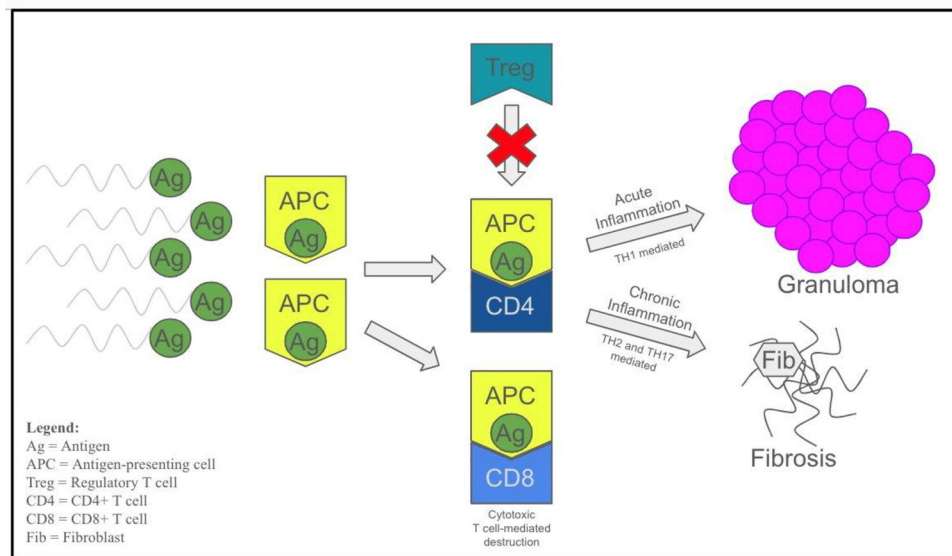


**Figure 1.** Pathogenesis of HP. Inhaled environmental antigens are recognized by APCs, stimulating a cytokine-mediated inflammatory response and MHC-mediated recruitment of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. A lack of regulatory T cells, particularly in patients with fibrotic HP, leads to exaggerated T-cell response. During the acute phase, differentiation of CD4 T cells to the Th1 subtype results in formation of granulomas, whereas chronic inflammation, mediated by Th2 and Th17 T-cell subtypes, results in fibroblast activation and deposition of extracellular matrix. A cytotoxic T-cell response is also stimulated via activation of CD8<sup>+</sup> T cells. HP = Hypersensitivity pneumonitis; APC = antigen presenting cell; MHC = major histocompatibility complex; Th = T helper.

with subsequent exposures.<sup>1,7</sup> Subacute and chronic HP tend to have more insidious presentations.<sup>2,7</sup> Subacute HP occurs when there is ongoing inflammation that leads to progressive respiratory symptoms. Symptoms and radiographic findings are often similar to other forms of ILD and can be difficult to distinguish without a detailed exposure history.<sup>7</sup> If early HP is unrecognized or uncontrolled, it may progress to chronic HP, which is characterized by the development of fibrosis in the absence of active inflammation.<sup>1,7</sup> This classification system has recently fallen out of favor due to the lack of clinical utility and prognostic value.<sup>4,9</sup> The 2020 American Thoracic Society /Japanese Respiratory Society /Asociación Latinoamericana del Tórax Clinical Practice Guideline<sup>9</sup> suggests categorizing HP into non-fibrotic HP (nfHP) or fibrotic HP (fHP) phenotypes because the presence of fibrosis is an independent risk factor for increased mortality.<sup>8</sup> The 5-year survival rate is estimated to be 25–30% in fHP.<sup>10</sup> The median survival reported in the literature ranges from 5 to 8 years in fHP compared with at least 16 to 21 years in nfHP.<sup>5,8</sup> Other poor prognostic factors include failure to remove inciting agent, older age, male sex, and tobacco use.<sup>11</sup>

### Pathogenesis

HP is a complex disease that involves both type III and IV hypersensitivity reactions.<sup>12</sup> Initial antigen exposure may lead to an immune-complex-mediated reaction, whereas repeated exposure causes a delayed hypersensitivity reaction. Most individuals develop

immune tolerance to commonly encountered environmental antigens mediated by regulatory T cells, which have been found to be reduced in patients with fHP.<sup>13,14</sup> Individuals who are genetically susceptible exhibit an exaggerated T cell-mediated immune response to inhaled antigens.<sup>7</sup> Genetic polymorphisms in class II major histocompatibility complex molecules have been implicated in the development of HP, potentially leading to differences in lung homeostasis, wound repair, and telomere-related gene mutations.<sup>11,13</sup>

Antigens are inhaled and recognized by the innate immune system *via* antigen-presenting cells (APC), including alveolar macrophages and dendritic cells.<sup>7,13</sup> Pattern-recognition receptors, including Toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and dectins, are activated in response to antigens and signal the release of proinflammatory cytokines. Antigens are then phagocytosed and presented *via* major histocompatibility complex molecules on the surface of APCs, which leads to recruitment of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes. CD4<sup>+</sup> cells can differentiate into T helper (Th) type 1, Th2, and Th17 cells, all of which play a role in HP. Th1 lymphocytes are present in the acute phase and can accumulate in lung tissue to form granulomas. Th2 and Th17 cells have been implicated in chronic inflammation and may contribute to fibrosis through fibroblast activation and extracellular matrix deposition (Fig. 1).<sup>7,13,14</sup>

A recent study discovered novel subtypes of peripheral blood monocytes in patients with fHP, including S100

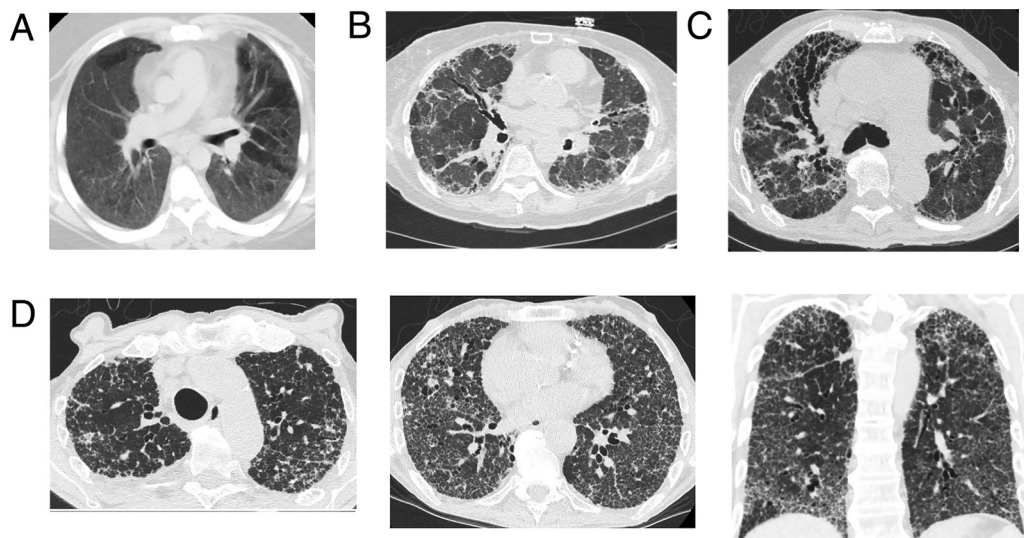


**Figure 2.** Radiographic phenotypes of HP. (A) Typical nonfibrotic HP: diffuse centrilobular ground-glass nodules and mosaic attenuation; (B) typical fibrotic HP: ground-glass opacities, air trapping, and traction bronchiolectasis in a diffuse distribution; (C) a variant pattern (compatible with fibrotic HP pattern): subpleural honeycombing with air trapping; and (D) a variant pattern (indeterminate for HP pattern): basal-predominant disease with homogeneously distributed ground-glass opacities, reticulation, and traction bronchiolectasis without honeycombing that resembles nonspecific interstitial pneumonia. HP = Hypersensitivity pneumonitis.

calcium binding protein A and chemokine ligand 3/4.<sup>14</sup> Trajectory analysis revealed that these monocyte subtypes differentiate into secreted phosphoprotein 1 macrophages, which are known to be profibrotic. The study also found a higher expression of certain granzyme subtypes in cytotoxic T cells of patients with fHP compared with healthy controls and idiopathic pulmonary fibrosis (IPF). This specific subpopulation of granzymes is enriched in proinflammatory cytokine pathways and may explain differences in immune etiology of fHP versus IPF. T-cell-mediated immunity plays a major role in the development of HP, but a humoral-mediated immune reaction through immunoglobulin G (IgG) immunocomplexes may also contribute to tissue injury by activating the complement system.<sup>13</sup>

## DIAGNOSIS

### Imaging

The optimal imaging modality for the evaluation of HP is high-resolution computed tomography (HRCT) of the chest without intravenous contrast. The study protocol should include thin slices (<1.5-mm thickness) taken at deep inspiration and after full expiration by using a high-spatial frequency reconstruction algorithm. HRCT findings associated with nfHP include diffuse distribution of ground-glass opacities, mosaic attenuation, centrilobular nodules, and air trapping (Fig. 2A).<sup>9</sup> The HRCT pattern of fHP is characterized by coarse reticulation, traction bronchiolectasis, and, in severe cases, honeycombing (Fig. 2B). Distribution is typically diffuse with basal sparing but can be lower lobe predominant in some variants.

Ground-glass opacities, centrilobular nodules, and air trapping may be superimposed on the fibrotic features.<sup>9</sup> The three-density sign, a combination of normal lung, ground-glass opacities, and air trapping,<sup>15</sup> is highly specific for fHP and is helpful in differentiating it from IPF.<sup>16</sup> There are various indeterminate patterns for fHP, including usual interstitial pneumonia, fibrotic nonspecific interstitial pneumonia, and organizing pneumonia (Fig. 2, C and D).<sup>9</sup>

### Pulmonary Function Tests

Pulmonary function test results can be variable in HP, and no pattern is diagnostic. A restrictive ventilatory defect and reduced diffusing capacity are common, as in other ILDs, but obstructive or mixed obstructive and restrictive patterns can be seen.<sup>17</sup> Although pulmonary function tests have limited utility in the diagnostic evaluation of HP, they can be useful for assessing baseline severity of disease, monitoring progression, and predicting prognosis.<sup>18</sup>

### History and Environmental Antigen Identification

Identifying an inciting antigen exposure begins with a comprehensive history, including timing, duration, and frequency of exposure as well as temporal relation to symptom onset. An environmental history should include questions with regard to the patient's home, type of air conditioning, hobbies, exposure to birds, and occupation. Bird and occupational exposures specifically have been associated with increased odds of developing HP.<sup>19</sup> An occupational history should start with

the most recent employment and work backward to uncover exposures such as farming, welding, sandblasting, food manufacturing, painting, gases, or fumes. Careful attention should be given to a history of flooding or other water damage in the home or workplace, which may raise suspicion for mold-induced HP.<sup>20</sup> Hobbies and activities such as gardening, composting, using hot tubs and/or saunas and/or pools, metal working, wood working, and playing wind instruments should also be surveyed.

Various questionnaires have been used to assist in the identification of exposures associated with ILDs, but a majority of these were adapted from asthma assessments, do not quantify the degree or duration of exposure, and have not been clinically validated.<sup>21</sup> In 2020, Barnes *et al.*<sup>22</sup> published an assessment tool specific for chronic HP that included 18 potential exposures based on Delphi consensus among ILD experts. This was subsequently tested in patients with chronic HP and elicited exposures in 33% of patients in whom a clinician could not, and increased the diagnostic confidence in cases of low-confidence chronic HP.<sup>23</sup> To account for differences in regional exposures, experts recommend using a questionnaire relevant to the patient's geographic location.<sup>24</sup>

### Serologic Testing

Peripheral blood testing for IgG antibodies against suspected precipitating antigens can be helpful in the diagnosis of HP. In a systematic review, Jenkins *et al.*<sup>25</sup> found that serum IgG testing in participants who were exposed to an antigen was able to differentiate those with HP from exposed control subjects without disease, with a sensitivity and specificity of 90% and 91%, respectively. In a study that involved patients with bird fanciers' lung, higher levels of IgG antibodies against relevant antigens were more closely associated with HP and IgG levels decreased with antigen avoidance.<sup>26</sup>

Despite its apparent utility, the clinical value of serologic testing is limited due to inconsistencies between available tests and common environmental exposures, particularly with respect to mold antigens. Sothorn *et al.*<sup>27</sup> cultured air samples from homes of patients with respiratory symptoms and suspected mold-related conditions. Among the most common molds identified, five were of the *Penicillium* genus and three were of the *Aspergillus* genus. Of these, only one of the *Aspergillus* species had a corresponding serum test available.<sup>27</sup> This highlights the challenge that serologic tests may not always confirm suspected precipitating exposures, and their reliability can be affected by geographic variations in prevalent mold species or other antigens.

### Bronchoscopy and Lung Biopsy

The utility of bronchoscopy for the diagnosis of ILDs is debated. Characteristic bronchoalveolar lavage (BAL)

cell differential patterns have been described for various ILDs, with HP being one of many associated with a lymphocytic pattern.<sup>28</sup> However, a more recent study showed that a mixed cellular pattern was most common overall, regardless of the HRCT pattern. There was no significant association between characteristic HRCT findings of HP (ground-glass opacities, three-density pattern, or mosaic attenuation) and BAL lymphocytosis > 20%.<sup>29</sup> Current clinical practice guidelines still recommend bronchoscopy for BAL with lymphocyte cellular analysis as part of diagnostic evaluation, with a threshold of 30% lymphocytosis considered to be significant.<sup>9</sup> In addition, flow cytometry may be considered for clinically suspected lymphocytic ILD or when BAL lymphocytosis is discovered during workup of ILD. CD8<sup>+</sup> lymphocyte predominance that results in a low CD4:CD8 ratio has been described in HP, whereas a high CD4:CD8 ratio (4:1 or greater) may be found in sarcoidosis.<sup>30</sup> However, these findings are inconsistent, may change over the disease course, and do not reliably discriminate different ILDs from one another.<sup>31</sup>

Transbronchial forceps lung biopsy or cryobiopsy should be considered to increase diagnostic confidence, with surgical lung biopsy reserved for rare cases when results from other diagnostic tests are inconclusive.<sup>9</sup> Characteristic histologic findings for nHP include lymphocytic bronchiolitis and poorly formed non-necrotizing granulomas. In fHP, the histologic features include airway-centered fibrosis, bridging fibrosis from center to periphery, and occasional honeycombing.<sup>9</sup>

### Multidisciplinary Discussion

As discussed, the diagnosis of HP requires the integration of HRCT findings, a thorough medical history with careful attention to environmental exposures, serologic testing for common antigens, BAL cellular analysis, and pathology (when available).<sup>9</sup> The final diagnosis should be made through multidisciplinary discussion that involves an ILD pulmonologist, thoracic radiologist, and pathologist when histology is available. Multidisciplinary discussion provides expert analysis of noninvasive tests to establish a provisional diagnosis before consideration of invasive diagnostic procedures.<sup>9,32</sup>

### TREATMENT

The cornerstone of treatment for HP is the identification and avoidance of the inciting antigen.<sup>2,11,33–36</sup> Other therapies include various immunomodulators and, for progressive fibrotic forms of HP, antifibrotic therapy, and, in some cases, lung transplantation.<sup>2,37</sup> To date, no consensus guidelines exist for the treatment of HP.

### Antigen Identification and Avoidance

Antigen identification and avoidance is of critical importance in the treatment and prognosis of HP.<sup>6,33</sup> In a

landmark 2013 study, survival in HP was significantly better when the inciting antigens were identified. The median survival was 18.2 years when the antigen was identified versus 9.3 years when unidentified.<sup>33</sup> This benefit persisted even in fHP but was less pronounced: 8.75 years when identified versus 4.88 years when unidentified. Identification of an inciting antigen is associated with a shorter duration of corticosteroid use and less reliance on steroid sparing agents.<sup>33</sup> Once the environmental exposure has been identified, complete avoidance is recommended, even though it can be burdensome for patients.<sup>34</sup> Several studies have shown that transplantation-free survival is better in patients who completely avoid antigens compared with those who do not.<sup>34–36</sup> Avoidance of inciting antigens may also improve lung function measured by forced vital capacity (FVC), especially in those with nfHP and mild fibrosis.<sup>35</sup> In some patients, however, progression of fibrosis occurs despite complete antigen avoidance.<sup>36</sup>

Despite the impact on disease prognosis, antigens remain unidentified in 30–50% of patients.<sup>33,36</sup> Identification of inciting antigens is particularly challenging in chronic forms of HP.<sup>3,33</sup> Serum antibodies may aid in identifying antigens, and industrial hygienists can help confirm environmental exposures. However, antigen identification can often be achieved through a thorough exposure history, especially when conducted by an ILD specialist. A retrospective study demonstrated that antigen identification through clinical history alone, when obtained by an experienced clinician, provided a transplant-free survival benefit.<sup>3</sup>

## Corticosteroids

Corticosteroids remain the primary pharmacologic treatment for HP, although data that support their use are limited.<sup>37,38</sup> The only randomized control trial that examined the efficacy of corticosteroids in HP was conducted in 1992, which involved 36 patients with farmer's lung. It showed improvement in FVC for up to 1 year and diffusion capacity for carbon monoxide (DLCO) up to 2 years with prednisolone taper over 8 weeks compared with placebo. These changes were not sustained, and there was no difference in mortality with the use of corticosteroids.<sup>39</sup> Subsequent retrospective studies have produced conflicting results. De Sadeleer *et al.*<sup>37</sup> found no survival benefit when steroids were used in nfHP and fHP but did reveal a significant improvement in FVC with steroid use in the nfHP group. Ejima *et al.*<sup>40</sup> demonstrated a survival benefit and improvement in FVC with prednisolone use when cohorts were matched for baseline age, lung function, and the presence of fibrosis. Results of several studies suggest that corticosteroids and other pharmacotherapy are initiated after lung function rapidly declines, which could explain the lack of survival

benefit when groups are unmatched for baseline lung function.<sup>37–41</sup>

Prednisone dosing typically starts at 0.5–1.0 mg/kg/day, up to 60 mg/day for 1–2 weeks in acute HP, or 4–8 weeks in subacute or chronic HP, followed by a taper based on physician guidance.<sup>6,38</sup> Specific recommendations with regard to the timing of corticosteroid initiation in HP are lacking.

## Steroid Sparing Agents

Azathioprine (AZA) and mycophenolate mofetil (MMF) are frequently used as second-line therapies in chronic HP due to evidence primarily adapted from studies of connective tissue disease associated ILD. The supporting evidence for their use in HP remains weak. Results of some retrospective studies suggest that AZA helps to preserve or improve FVC at 12<sup>43,44</sup> and 24 months,<sup>44</sup> whereas others have shown improvement in DLCO and reduction in prednisone dosage with MMF or AZA use.<sup>42,45</sup> Both drugs were tolerated overall, with 14.3% experiencing adverse effects, most commonly gastrointestinal issues.<sup>42</sup> These agents are typically introduced after symptoms or lung function worsen on steroid therapy. Retrospective studies have shown that adding steroid-sparing agents to prednisone resulted in similar survival and lung function outcomes compared with prednisone monotherapy<sup>10,41</sup> but with fewer adverse events, which suggests a potential benefit to earlier MMF or AZA use.<sup>10</sup> Rituximab is less commonly used but may lead to stabilization or improvement in FVC in patients with declining lung function.<sup>46</sup>

## Antifibrotic Therapy

Compared with nfHP, fHP has worse survival outcomes but the degree of fibrosis can vary widely.<sup>8,9</sup> Some patients may go on to develop progressive pulmonary fibrosis (PPF), which has a similarly poor survival as IPF. In patients with PPF, a relative decline in FVC of at least 10% is the strongest predictor of reduced transplantation-free survival.<sup>47</sup> Given the poor prognosis at this stage, effective therapies are urgently needed. The INBUILD trial showed that nintedanib reduced the rate of FVC decline in patients with non-IPF progressive fibrosing ILDs (including HP) compared with placebo.<sup>48</sup> This effect was not diminished by the use of immunosuppressive therapy, which suggests that combination therapy may be effective.<sup>49</sup> In contrast, studies that used pirfenidone in chronic HP and PPF did not show the same benefits.<sup>50,51</sup>

## Lung Transplantation

In cases of patients with progressive fHP, lung transplantation should be considered.<sup>6</sup> Compared with IPF, patients with fHP have reduced adjusted risk of death and excellent 1-year survival rates, of 96%.<sup>52</sup>

## Short Telomere Syndrome

Short telomere syndromes (STS) are associated with the development of pulmonary fibrosis (PF), including chronic HP.<sup>53</sup> Reduced age- and sex-adjusted leukocyte telomere length has been associated with increased mortality in patients with PF.<sup>54</sup> Ley *et al.*<sup>55</sup> demonstrated a reduced transplantation-free survival in patients with chronic HP and with STS. Shorter telomere length is also associated with more extensive fibrosis in patients with chronic HP. HP is most commonly associated with the telomerase reverse transcriptase (*TERT*) and regulator of telomere elongation helicase 1 (*RTEL1*) mutations responsible for telomere length.<sup>56</sup> Although use of immunosuppression in IPF has been associated with increased mortality,<sup>57,58</sup> it is unclear if this holds true for chronic HP, given the immune-mediated pathway to fibrosis. A prospective study that evaluated the efficacy of MMF in patients with chronic HP found improved survival rates in patients with normal telomere lengths who received MMF but a lack of survival benefit in those with shorter telomere lengths.<sup>59</sup> Assessing telomere length in patients with HP may provide valuable prognostic information and guide therapeutic decisions, but more data are needed.

## CONCLUSION

HP is an ILD that occurs in individuals who are susceptible and who develop an exaggerated immune reaction to inhaled environmental antigens.<sup>1,2</sup> Persistent inflammation may lead to a fibrotic form of HP, which is associated with poor survival outcomes.<sup>13,14</sup> Accurate diagnosis and early treatment are important in limiting progression to fibrosis. However, a diagnosis of HP is challenging due to its heterogeneity and rarity.<sup>4,5</sup> Symptoms and radiographic features often overlap with other ILD types.<sup>1,7</sup> Therefore, a high index of suspicion for HP is necessary. Once HP is suspected, multidisciplinary discussion of clinical history, imaging, BAL, and histopathology is recommended.<sup>9</sup> Although steroids and immunosuppressive agents are frequently prescribed,<sup>2</sup> antigen avoidance is the only treatment with a proven mortality benefit and thus is the mainstay of HP treatment.<sup>6,32</sup> Unfortunately, an inciting antigen cannot be identified in 30–50% of patients.<sup>32,36</sup> Serologies are not available for every HP-associated antigen,<sup>27</sup> and an accurate diagnosis often relies on knowledge of regional antigens and experience in obtaining a thorough environmental history. Questionnaires about HP-related environmental factors tailored to a patient's geographic region can improve antigen identification rates.<sup>21,23</sup> Although consensus guidelines<sup>9</sup> with regard to a diagnosis of HP have recently been published, treatment guidelines are still lacking. Further research is needed to determine the efficacy of current pharmacotherapy options, appropriate timing of immunosuppression

initiation, and duration of therapy. In addition, the discovery of immune cell perturbations may pave the way for targeted immunotherapies, and further investigation into the role of STS and its impact on treatment strategy is warranted.<sup>14,59</sup>

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